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Protolytic Equilibria in Tetrazoles

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Abstract—Published data on protolytic equilibria involving tetrazole hetero ring are summarized. The information is systematized according to the types of protolytic equilibria.

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1. INTRODUCTION

Tetrazole ring structure is abnormal. The nitrogen content in an unsubstituted tetrazole is 80% of the total weight of the molecule, the largest figure among the stable ubsubstituted heterocyclic systems. In this feature tetrazole surpasses tetrazine and is inferior only to some unstable heterocyclic systems practically nonexistent in free state: pentazoles, pentazines etc. Despite this extremely high nitrogen content in the ring the unsubstituted tetrazole, and also most of its derivatives, is endowed with relatively high stability with respect to heating and microwave irradiation, and also to various chemical reagents (oxidants, reducers, acids, bases, alkylating agents, dienophiles, etc.). Tetrazole fragment is virtually lacking in the naturally occurring molecules, yet the presence of tetrazoles in the metabolism products of some protozoa is mentioned [1]. It is presumable however that tetrazole alongside the other abnormal polynitrogen heterocycles may form under conditions of the other planets of Solar system or their satellites containing in the composition of the atmosphere or on the surface hydrocarbons and nitrogen [1]. If this assumption will be confirmed, it will turn out that tetrazoles will not be a natural rarity.

The practical applications of tetrazoles are extremely versatile. Inasmuch as the tetrazole ring is an isoteric analog of carboxy and *cis*-amide groups this heterocyclic moiety is successively used in the synthesis of antimetabolites of a large number of natural molecules [2, 3]. Tetrazole moiety is present in the composition of some widely known newest drugs: bactericidal (Kefzol), cardiovascular (Losartan) medicines, and some others [1–3]. Tetrazole possesses a high enthalpy of formation: its decomposition results in liberation of two nitrogen molecules and a significant amount of energy. Therefore the derivatives of this series are exploited as explosives, missiles propellants components, and gas generators [4, 5]. The products of exhaustive N-alkylation of 5-substituted tetrazoles are used in the chemical synthesis as

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The field of scientific interests is the physicochemical properties and reactivity of nitrogen-containing aromatic heterocycles.

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The field of scientific interests is the synthesis, physicochemical properties and reactivity of nitrogen-containing heterocycles.

phase transfer catalysts [6, 7]. Among the other tetrazole features it should be specially stressed that they are capable of forming stable complexes with metal ions. This ability is successfully used in analytical chemistry, in the systems for removal of heavy metal ions from liquids, and in chemical systems for metal protection against corrosion [8–10]. Due to the extensive development of convenient and easily scaled synthetic methods increasing the availability of tetrazoles the interest to the compounds of this class permanently grows: Every year the number of publications treating tetrazoles notably increases.

Many physical, chemical, physicochemical, and biological properties of tetrazoles are closely related to their ability to behave as acids and bases. In the tetrazole ring all the four nitrogen atoms connected in succession are able to be involved in protolytic processes. Tetrazole ring is to the same extent abnormal in the structure and unique in acid-base characteristics. For instance, compared to the other thermally and chemically stable azoles the tetrazoles possess abnormally high acidity and very weak basicity. Since the mid-XX century and up till now the acidity, basicity, and prototropic tautomerism of tetrazoles were the subjects of research by various scientific teams. The Soviet, later Russian, scientists made a considerable contribution into the investigation of protolytic equilibria involving tetrazoles. Some of the studies in this field were summarized in reviews and monographs dedicated to tetrazoles or protolytic equilibria of the nitrogen-containing heterocycles [1, 11–26]. However in the majority of reviews on this topic the thorough consideration was directed only to a part of the possible protolytic equilibria involving the tetrazole ring, but at the same time some of these processes suffered concise treatment or were totally disregarded. A considerable number of surveys on this topic were published more than 10 years ago. Yet within the last decade new original investigations appeared in the field of tetrasoles protoilytic equilibria extending and providing better insight of the subject. Among these studies especially important is the research carried out with the use of modern theoretical methods. These studies provided an understanding of many features of the protolytic equilibria involving the compounds of this series, and revealed some general laws.

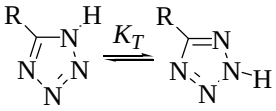
This review is focused on the publications that appeared in the last decade and also on the studies overlooked by some reasons in the preceding surveys and monographs. We attempted to join up various types of protolytic equilibria involving the tetrazole ring. We hope that this survey will become a convenient reference source for researchers working in the field of the chemistry of nitrogen-containing heterocycles.

2. ANNULAR TAUTOMERISM

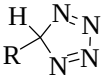
2.1. *Tautomerism of Neutral NH-Unsubstituted Tetrazoles*

Neutral NH-tetrazoles with no functional substituents at the carbon atom of the hetero ring can exist in the form of 1*H*- and 2*H*-tautomers (Scheme 1).

Scheme 1.



It is presumable theoretically that a hypothetical nonaromatic 5*H*-form also exists However up till now no experimental method detected this species.



According to calculations by MP2 method the 5*H*-form of unsubstituted tetrazole possesses a very high energy and is improbable by thermodynamical reasons [27, 28]. However these species may be presumed as highly reactive short-lived intermediates in some chemical transformations of nitrogen-containing heterocycles [29, 30].

1*H*/2*H*-Tautomerism of tetrazoles since nineteen fifties has been the object of detailed experimental and theoretical studies. The early experimental results in this field are sufficiently comprehensivey treated in several reviews and monographs [1, 11, 12, 14, 22, 24–26]. This type of tetrazoles protolytic equilibria was experimentally investigated in solutions and in a gas phase. The prevailing tautomers of 5-substituted tetrazoles were established also in the crystalline state. The following methods were applied to these studies: In solutions was used NMR spectroscopy on different nuclei (^{1}H, ^{13}C, ^{14}N, ^{15}N), UV spectroscopy, and also the comparison of dipole moments and acidity constants with those of model compounds; in the gas phase was employed microwave, photoelectron, and mass spectroscopy; the crystalline compounds were investigated by IR and NMR spectroscopy and X-ray crystallography. Let us consider the main conclusions on this problem based on experimental results.

According to X-ray diffraction analysis, vibrational spectroscopy, and ^{13}C NMR spectra 1*H*-tetrazole and its derivatives in crystals exist as individual 1*H*-tautomer

[1, 12, 25, 31–36]. However some 5-R-tetrazoles are likely to form hybrid crystals containing both 1*H*- and 2*H*-tautomers. Note that the 1*H*-form is additionally stabilized in the crystal by hydrogen bonds N–H···N resulting in dimers, trimers, and other agglomerates [1, 12, 14, 31, 35].

Various physicochemical methods revealed that in solutions prevailed the more polar 1*H*-tautomer [1, 11, 12, 14] (Table 1). Yet it was shown that in some 5-substituted tetrazoles the content of the 2*H*-tautomer in solution reached 15–20% [1, 12, 16, 37]. The increased content of the 2*H*-form can arise in the following events: (1) at reduced dielectric permittivity of the medium (because in solvents of low polarity the solvation of more polar 1*H*-form is reduced [38, 39]); (2) at increased electron-withdrawing property of the substituent in the position *5* (it has been previously suggested that it has been determined by different character of conjugation between the substituent and tetrazole ring [37], but later it has been shown to depend only on solvation effects, see further); (3) at the influence of sterical effects of substituent attached to the carbon of the heterocycle (introducing bulky substituents into the *ortho*-position of the benzene ring in the 5-aryltetrazoles results in increased content of the 2*H*-tautomer [1, 12]) (Table 1). The shift of the tautomeric equilibrium presented in Scheme 1 can be considerably affected by formation of intra- and intermolecular hydrogen bonds involving the protons of NH groups of the hetero ring [1, 12].

The most important and reproducible results in solutions were obtained by dipole moments method and by ^{13}C and ^{15}N NMR spectroscopy [1, 11, 12, 37, 40, 41]. It proved that just NMR spectra and dipole moments of different tautomeric forms of NH-unsubstituted tetrazoles have the most characteristic distinctions. 1*H*-Tetrazoles posess as a rule a larger dipole moment compared to the 2*H*-forms. For instance, the values of dipole moments (μ) of some N-alkyltetrazoles in benzene and dioxane were 5.46 D (1-ethyltetrazole), 2.46 D (2-ethyltetrazole) [42], 5.88 D (1-methyl-5-phenyltetrazole), and 2.52 D (2-methyl-5-phenyltetrazole) [40]. According to the experimental findings the dipole moments of NH-unsubstituted tetrazoles and 1-alkyl-tetrazoles in solutions have close values (for tetrazole μ 5.14 D [40]). The proton signals from α-methylene groups of 2-alkyltetrazoles in the ^1H NMR spectra are observed downfield from the corresponding signals of the 1*H*-isomers [1, 12]. Even more spectacular is the difference between these isomers in the ^{13}C NMR spectra. The chemical shift of the heterocyclic carbon is 143–144 and 153–154 ppm for 1-alkyl- and 2-alkyltetrazoles respectively [43], 153.2 and 163.8 ppm for 1- and 2-methyl-5-phenyltetrazole respectively [44, 45]. Chemical shifts of nitrogen atoms in the ^{14}N and ^{15}N NMR spectra of 1*H*- and 2*H*-tetrazoles also are considerably different [1, 46] and dissimilarly sensitive to solvent [47]. The NMR spectra of NH-unsubstituted tetrazoles in solutions are mostly similar to the spectra of 1-alkylisomers confirming the prevalence of the 1*H*-form.

Table 1. Some data on tautomer composition of NH-unsubstituted 5-R-tetrazoles in solutions [1, 12, 14]

R	Fraction of 1*H*-tautomer, %	Analytical method	Solvent
H	78–85	Dipole moments	Dioxane
H	85	^1H NMR	Acetone
H	100	^{13}C NMR	DMF, DMSO, acetone, water
H	90–99	^{15}N NMR	DMSO
MeS	85–87	^{13}C, ^{15}N, ^1H NMR	DMSO
2-tolyl	86 73	^{13}C NMR	DMSO Dioxane
2,6-dichlorophenyl	91 68	^{13}C NMR	DMSO Dioxane

According to the data of photoelectronic, mass, and microwave spectroscopy, and also of some other methods the 2*H*-tautomer prevails in the gas phase [16, 18, 24, 25, 30, 48–50]. However, some studies revealed the simultaneous presence in the gas phase both of 1*H*- and 2*H*-forms of 5-R-tetrazoles (R = H, CH_3, CD_3, CF_3, NH_2) [16, 18, 25].

Starting from nineteen seventies the annular tautomerism of tetrazoles has become an object of numerous theoretical studies. To this end versatile semiempirical methods of quantum chemistry were exploited: CNDO, MNDO, MNDO/M, AM1, PM3 [51–56]. It was shown that semiempirical methods could not adequately describe the tetrazoles tautomerism: the results of these calculations disagreed with experimental findings. The reason of the discrepancy may lie in the underestimation of the mutual repulsion of the unshared electron pairs of vicinal nitrogen atoms of the hetero ring that finally leads to wrong estimation of a tautomer energy [56]. As seen in Fig. 1, in 1*H*-tetrazoles two interactions of the unshared electron pairs are possible, whereas in 2*H*-tetrazoles, only one.

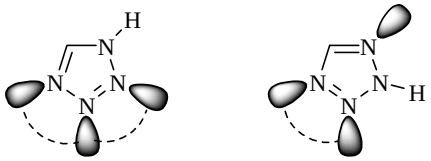


Fig. 1. Mutual repulsion of unshared electron pairs in the 1*H*- and 2*H*-tautomers of tetrazole.

Yet the semiempirical methods AM1, PM3, and MNDO fairly well describe the electron density distribution and dipole moments of tetrazoles [55]. PM3 procedure was also successfully applied to the calculation of thermochemical parameters of 5-substituted tetrazoles [51]. In describing the tautomerism of tetrazoles a better agreement with the experiment was obtained using ab initio calculations [27, 38, 39, 50, 56–65]. However the results of calculation by these procedures essentially depend on the choice of the basis set [50]. For instance, at calculations by HF method only those performed with the basis 3-21G and higher show that in the gas phase the 2*H*-form of unsubstituted tetrazole is more energetically favorable than 1*H*-form. The energy difference between these tautomeric forms equals commonly 2–3 kcal mol^{-1}. A better agreement with the experiment is achieved at the use of extended basis sets [27, 38, 56, 58, 64]. Therewith the results of calculations by methods HF, DFT, and MP are in a fair agreement [27, 38, 59, 61, 63]. The calculations by MP2 method of the thermodynamical characteristics of tetrazole showed that although the 2*H*-form is more favored in the gas phase, at growing temperature the thermodynamical stability of the 1*H*-tautomer increased [63].

Theoretic investigation of the influence on the tautomeric equilibrium (Scheme 1) of solvation effects was performed by HF, DFT, and MP methods [27, 38, 39, 66]. It was shown in the publications cited that solvation to a stronger extent decreased the energy of 1*H*-tautomer as compared to 2*H*-tautomer, and this effect is the more pronounced, the greater is the dielectric permittivity of the simulated medium. It was indicated that in the media of low polarity, like in the gas phase, the thermodynamical stability of the 2*H*-form of unsubstituted tetrazole is higher, than that of the 1*H*-form. In theoretical calculations of the solvation energy of tetrazole tautomers the extended basis sets are preferable including polarization and diffuse functions, e.g., 6-31++G** [38, 63].

In the majority of theoretical studies in this field until recently only unsubstituted heterocycle was considered. However results were published lately of investigations on the tautomerism of some 5-substituted tetrazoles carried out with the use of nonempirical methods in extended basises [39, 57, 60–62, 65]. It was shown in these studies that in all 5-R-tetrazoles in question (R = Hlg, Alk, Ph, NH_2, N_3, NO_2, OMe) in the gas phase the 2*H*-tautomer was the more stable: 2*H*-Form was usually by 1.5–4.0 kcal mol^{-1} more thermodynamically preferable than the 1*H*-form [61, 65] and the substituent in the ring insignificantly affected the energy difference. As follows from the calculations B3LYP/6-31G** in the case of tetrazol-5-ylcarboxylic acids and their esters the annular tautomerism might be affected by intramolecular interactions between the tetrazole ring and the carboxy group [67]. Using method DFT (B3LYP/6-31G*) on a series of 5-R-NH-tetrazoles in a gas phase we demonstrated that the aromaticity of the ring significantly grew on going from 1*H*- to 2*H*-prototropic form [65]. Similar conclusions on the aromaticity of unsubstituted tetrazole tautomers and certain 5-substituted tetrazoles were formulated in [61, 68].

In contrast to the relative energy the dipole moments of 1*H*- and 2*H*-tautomers of 5-R-tetrazoles significantly depend on the character of the substituent in the position 5 (Fig. 2) and correlate with the σ_p constants of the substituent

$$\mu_{1H} = 5.40 - 2.56\,\sigma_p,\ r\ 0.968,\ s\ 0.27,\ n\ 7 \qquad (1)$$

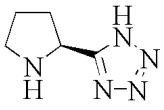
$$\mu_{2H} = 2.33 + 2.72\,\sigma_p,\ r\ 0.962,\ s\ 0.31,\ n\ 7. \qquad (2)$$

Especially large difference in dipole moments of 1*H*- and 2*H*-forms was found for electron-donor substituents. On increasing the electron-withdrawing character of the substituent the dipole moment of the 2*H*-form grew, whereas that of the 1*H*-tautomer decreased, and 2*H*-tautomer of 5-nitrotetrazole proved to be the most polar. Thus we can expect that in polar media the 1*H*-forms of 5-R-tetrazoles containing electron-donor substituents should be better solvated whereas for the 5-nitrotetrazole the 2*H*-form should be solvated better. Actually, as was shown in [39] using methods CPCM/HF/6-31+G* and CPCM/B3LYP/6-31+G*, the free energy of solvation of 1*H*-form on going from the unsubstituted tetrazole to 5-nitrotetrazole decreased by more than 1.5 kcal mol^{-1} whereas for the 2*H*-the opposite trend was observed: The solvation energy of 5-nitrotetrazole was by 3 kcal mol^{-1} higher than that of unsubstituted heterocycle.

It can be concluded from the above reasoning that just the solvation effects govern the different reactivity

and selectivity of certain chemical reactions of 5-R-NH-tetrazoles containing substituents of different nature at the carbon atom of the heterocycle. The above mentioned experimental findings on the growing fraction of 2*H*-tautomer in solutions at increased electron-withdrawing character of the substituent in the position *5* obviously is due only to the effect of the medium.

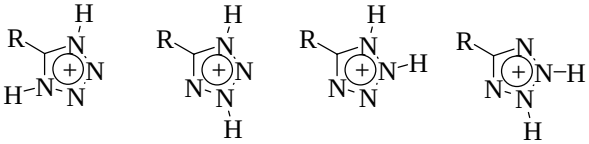
The results of [66] somewhat drops out of the general trend. It was reported that according to the theoretical calculations performed by DFT method in the basis B3LYP/6-31G** for 5-(pyrrolidin-2-yl)tetrazole in gas phase 1*H*-form proved to be more stable (by 2.3 kcal mol^{-1}) than the 2*H*-tautomer. Therewith the relative stability of the 1*H*-tautomer in DMSO increased to 3.3 kcal mol^{-1}.



The process of 1*H*/2*H*-tautomeric transformation (Scheme 1) is sufficiently fast and easily reversible if it proceeds by intermolecular mechanism involving the molecules of medium or the second heterocycle molecule [24, 69]. Thus, under conditions favoring the intermolecular proton transfer in the chemical or other transformations both prototropic forms or the form of higher reactivity can take part. Thus, in the study of the mechanism of unimolecular thermal decomposition of tetrazole and its 5-substituted derivatives it was demonstrated that both in the gas phase and in melts the decomposition mechanism corresponded only to the decomposition of the 2*H*-form although in the condensed phase initially prevailed the 1*H*-form [70].

2.1. *Tautomerism of Tetrazolium Ions*

Existence of four tautomeric forms of tetrazolium aromatic cation is theoretically presumable. The species are essentially different in thermodynamical stability. As was demonstrated in [58, 71, 72] applying *ab initio* calculations on the levels HF/6-31G*, B3LYP/6-311+G(3df,2p), G2(MP2), G3, 1*H*,2*H*$^+$- and 2*H*,3*H*$^+$-forms were by 15–20 kcal mol^{-1} thermodynamically less feasible than more stable 1*H*,3*H*$^+$- and 1*H*,4*H*$^+$-forms. The considerable destabilization of the 1*H*,2*H*$^+$- and 2*H*,3*H*$^+$-forms is due to the effect of mutual repulsion of vicinal NH-fragments in the heterocyclic system. This



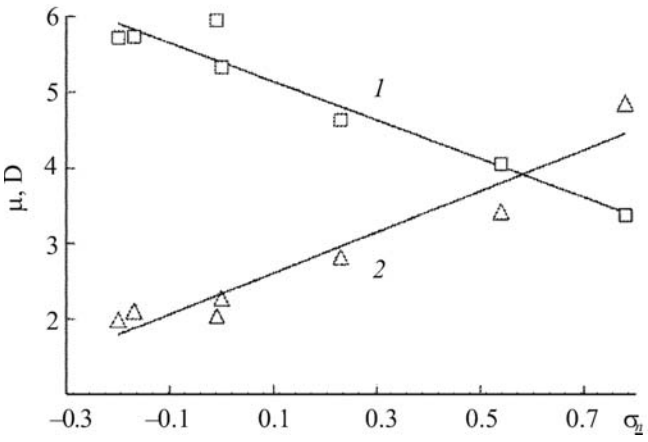
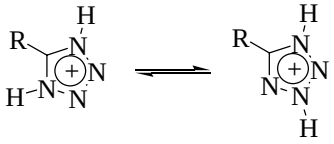


Fig. 2. Correlation of calculated (B3LYP/6-31G*) dipole moments μ of different tautomeric forms of 5-R-tetrazoles (R = H, Me, *t*-Bu, Ph, Cl, CF_3, NO_2) with the σ_p constants of substituents: *1*, for 1*H*-forms, *2*, for 2*H*-forms [65].

effect exists also in other azoles. For instance, the stability of pyrazolium cation where this interaction is present is significantly lower than that of its isomer imidazolium cation; this is seen in particular in notably lower basicity of pyrazole compared to imidazole [13].

Both experimental and theoretical methods demonstrated that the protonation of 1*H*- as well as of 2*H*-tetrazoles occurred at the nitrogen atom in the position *4* and resulted in formation of 1*H*,3*H*$^+$- and 1*H*,4*H*$^+$-tetrazolium ions respectively [16, 24, 52, 53, 73–81]. A tautomeric equilibrium is possible involving just these two forms (Scheme 2).

Scheme 2.



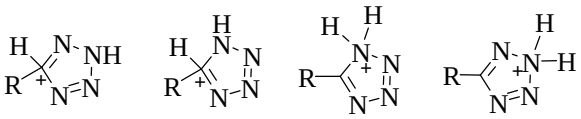
Thermodynamic stability of two tautomer is forms of the tetrazolium cation presented on Scheme 2 is approximately equal. However the 1*H*,4*H*$^+$-form is a little more thermodynamically preferable that the 1*H*,3*H*$^+$-form [82]. This in particular becomes apparent from the lower basicity of N^2-substituted tetrazoles whose protonation results in 1*H*,3*H*$^+$ tetrazolium cation than the basicity of the corresponding N^1-isomers that on protonation give 1*H*,4*H*$^+$-cations [16].

Total energy and thermodynamic characteristics of various prototropic forms of tetrazolium cations were

calculated both by semiempirical [52, 53, 74, 75, 83] and *ab initio* methods [58, 65, 71–73, 84]. Like for neutral 1*H*/2*H*-forms of tetrazole, the most suitable for calculation of tetrazolium cations proved to be nonempirical methods applying extended basis sets. In keeping with results of theoretical calculations performed by these methods for the unsubstituted tetrazole the 1*H*,4*H*$^+$-form is by about 2 kcal mol^{-1} thermodynamically more preferable than the 1*H*,3*H*$^+$-form [58], and this difference is the greater the lower the level of the basis set used. The calculations carried out employing the most extended basis sets [6-311+G(3df,2p), G2, G3] showed that this difference is still smaller [71, 72]. However the solvation energy of the 1*H*,4*H*$^+$-form is significantly higher compared to that of 1*H*,3*H*$^+$-tautomer [72]. Therefore the former type of cation should be better stabilized in solutions. 1*H*,3*H*$^+$-tautomer is more aromatic than 1*H*,4*H*$^+$-tautomer [65]. This fact can originate, in particular, from the lack of the effect of mutual repulsion of unshared electron pairs impossible for two contiguous nitrogens of "pyridine" type in the 1*H*,3*H*$^+$-tautomer of tetrazolium cation (Fig. 1); the effect of mutual repulsion essentially destabilizes the heterocyclic system [56]. The calculations performed by modern semiempirical procedures also indicate that protonation of 1*H*- and 2*H*-tetrazoles occurs prevailingly at the nitrogen in the position *4* of the hetero ring [52, 53, 83].

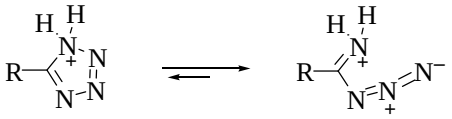
It was shown by calculating the effect of the substituent in the position *5* of the heterocycle on the tetrazolium cation tautomerism [65] by B3LYP/6-31G* method that the greater stability of the 1*H*,4*H*$^+$-form compared with the 1*H*,3*H*$^+$-form of tetrazolium cation existed only in the case of electron-donor substituents. The energies of 1*H*,3*H*$^+$- and 1*H*,4*H*$^+$-tautomers of unsubstituted tetrazole proved to be close. In the presence of electron-withdraw-ing susbstituents in contrast the 1*H*,3*H*$^+$-form of cation was preferable. For instance, 1*H*,3*H*$^+$-tautomer of 5-nitrotetrazole is more stable by 2 kcal mol^{-1} than the 1*H*,4*H*$^+$-tautomer. This effect was also confirmed by calculations carried out by procedures B3LYP/6-311+G(3df,2p) and G2(MP2) for the protonated forms of unsubstituted tetrazole and 5-nitrotetrazole [71]. A sterical effect of substituent in the position *5* practically does not affect the tautomerism of the protonated forms [65].

Besides the tetrazolium cations formed as a result of proton addition to an unshared electron pair of one of tetrazole nitrogen atoms without distortion of the heterocycle aromaticity it is possible theoretically suggest the existence of four nonaromatic cations.



We did not find any published experimental findings confirming the possibility of existence of such cations. Yet publications are known where the possibility of such species to exist is considered from the theoretical viewpoint [71, 72]. For instance, in [71] the total energy of 1*H*,5*H*$^+$- and 1*H*,1*H*$^+$-forms of unsubstituted tetrazolium cation was calculated using B3LYP/6-311+G(3df,2p) and G2(MP2) methods. According to the results of these calculations the 1*H*,5*H*$^+$-form is approximately by 50 kcal mol^{-1} less favorable than the most stable 1*H*,3*H*$^+$- and 1*H*,4*H*$^+$-tautomers of the tetrazolium cation. It was even impossible to optimize the 1*H*,1*H*$^+$-form in a cyclic structure: The heterocycle underwent opening leading to the corresponding protonated imidoyl azide (Scheme 3).

Scheme 3.



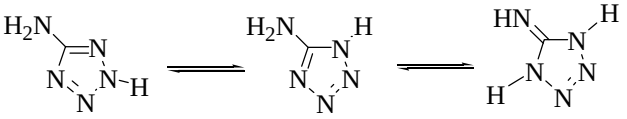
R = H, NO_2.

3. TAUTOMERISM INVOLVING FUNCTIONAL GROUPS

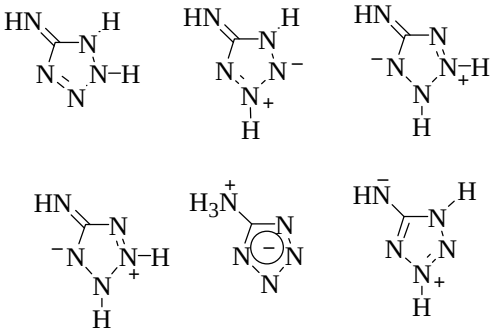
3.1. *5-Aminotetrazole and its Derivatives*

Protolytic equilibria of 5-aminotetrazole and its derivatives are complicated by amino-imino tautomerism (Scheme 4).

Scheme 4.

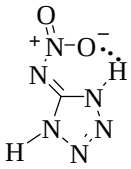


In turn, both amino and imino forms can exist as various annular tautomers. The number of such tautomers accounting also for the possible mesoionic and zwitterionic structures is very large. Some of them besides those shown in Scheme 4 are presented below.

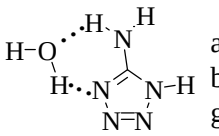


Many among these forms, although not observed experimentally, may be regarded as intermediates in some chemical reactions of 5-aminotetrazole and its derivatives [77, 85, 86]. Quantum-chemical calculations by MP2/6-31G* method showed that the mesoionic forms and structures with the vicinal position of the NH fragments are by 18 kcal mol^{-1} richer in energy than the forms presented in Scheme [85, 87]. Therefore the investigation of the prototropic tautomerism in 5-amino-tetrazoles results in consideration of the equilibrium in Scheme 4.

For a long time it remained unclear, in which form, amino or imino, the 5-aminotetrazole predominantly existed. It was shown by X-ray diffraction study that in the crystal this compound took the amino-1*H*-form [1, 12, 14]. The NMR and IR spectral data proved to be more difficult for interpretation. In keeping with the data obtained by these methods it was considered for a long time that in the solid state and in solutions the 5-amino-tetrazoles could exist both in amino and imino forms, and the contents of both forms were comparable and essentially depended on the character of the substituent at the exocyclic nitrogen and on the medium [11, 12, 14, 77, 85]. Nonetheless, later it was shown by means of NMR, Raman, and IR spectroscopy that many derivatives of 5-aminotetrazole same as 5-aminotetrazole itself in the crystalline state and in solutions exist predominantly in the amino form [1, 86, 88]. Exceptions to the rule may be compounds containing substituents at the nitrogen of the amino group capable of specific intramolecular or intermolecular interactions [25]. For instance, in the 5-nitroaminotetrazole the imino form may be additionally stabilized by the intramolecular hydrogen bond and may become prevailing [1].



According to calculations by MP2/6-31G* and B3LYP/LANL2DZ methods the amino form of 5-amino-tetrazole in the gas phase is more stable than the corresponding imino tautomer by over 18 and 9 kcal mol^{-1} respectively [87, 88]. The same qualitative result was obtained on accounting for the solvation effects [88]. The character of annular tautomerism of the 5-aminotetrazole is analogous to that described in the Section 2.1: The 2*H*-form is preferable in the gas phase, whereas considering the solvation effect the 1*H*-tautomer possessing the largest dipole moment becomes favorable in solution [39, 61, 88].

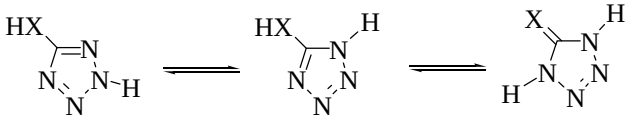


In solvation of 5-aminotetrazole, also in formation of the hydrogen bonds, both the hetero ring itself and the amino group are involved.

3.2. *5-Hydroxy- and 5-Mercaptotetrazoles*

5-Hydroxy and 5-mercaptotetrazoles and their N*1*-alkyl(aryl) derivatives can participate in keto-enol and thione-thiol tautomeric equilibria (Scheme 5). This ability provides the main distinctions in the chemical and physico-chemical properties of these compounds from the other 5-R-tetrazoles.

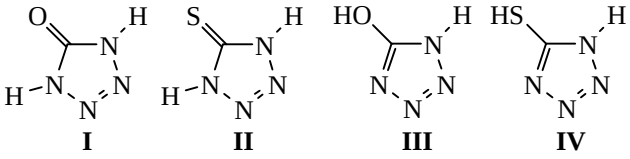
Scheme 5.



X = O, S.

This type of prototropic tautomerism of tetrazol-5-ones (thiones) is studied experimentally in sufficient detail. In contrast to amino-imino tautomerism practically all the researchers who investigated the equilibrium presented in Scheme 5 made a unique conclusion. As shown by X-ray crystallography, IR, Raman, UV, ^{1}H, ^{13}C, ^{15}N NMR, and photoelectron spectroscopy, and also by some other methods, tetrazol-5-ones (thiones) in a solid state, in solutions, and in a gas phase exist predominantly as 1,4-dihydro-tetrazolones (thiones) [1, 11, 12, 14, 25, 89–93]. In recent studies [94, 95] exploiting the Fourier IR spectroscopy 1-phenyltetrazol-5-one and 1-methyl-5-mercaptotetrazole were found to exist even in the matrix of solid argon at low temperature exclusively as 1-phenyl-1,4-dihydro-5*H*-tetrazol-5-one and 1-methyl-1,4-dihydro-5*H*-tetrazole-5-thione. These experimental results are well consistent with the data of calculations performed on the level of B3LYP/6-31++G**.

Table 2. Total energy and dipole moments of tautomeric forms of tetrazol-5-one and tetrazole-5-thione calculated by method HF/6-1G** [97]

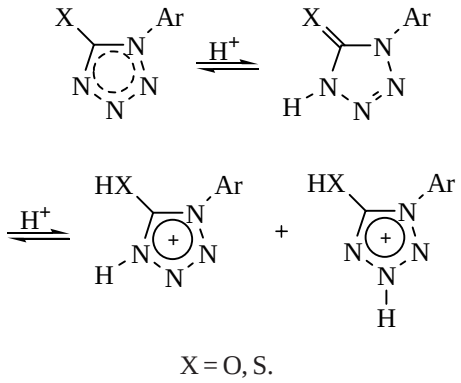


I **II** **III** **IV**

Form	*E*, a.u.	μ, D
I	–331.64467	0.81
II	–654.28516	2.33
III	–331.62915	4.62
IV	–654.26899	4.60

Besides the already mentioned several theoretical studies were focused on calculation of energy, geometry, and electronic structure of various tautomeric forms shown in Scheme 5. First among these publications was the paper of Postovskii and Kovalev where the calculations were performed by Hueckel method [96]. The good qualitative applicability of PM3 procedure for calculation of orbital energies in tetrazol-5-ones (thiones) was shown in [90]. The nonempirical calculations of enthalpy of formation of neutral 1*H*- and 2*H*-5-hydroxytetrazoles performed in the basis B3LYP/6-31G* demonstrated that the energy of 2*H*-form is slightly less than the energy of 1*H*-form [57]. In [97] the prototropic tautomerism of tetrazol-5-one (thione), 1-aryltetrazol-5-ones (thiones), and their cojugate acids in the gas phase was investigated by *ab initio* methods (HF/6-31G**) and AM1. The results obtained show that semiempirical calculations adequately agree with experimental findings and *ab initio* calculations only if a correction is made accounting for the mutual repulsion of the unshared electron pairs on the vicinal nitrogens in the hetero ring.

Scheme 6.



X = O, S.

These data also confirm that the most preferable in the gas phase are the corresponding tetrazol-5-ones (thiones) (Table 2) whose protonation occurs at the exsocyclic heteroatom leading to the formation of 1*H*,3*H*$^+$- and 1*H*,4*H*$^+$- tetrazolium cations of similar energy (Scheme 6).

5-Hydroxy and 5-mercapto forms of tetrazole possess considerably greater dipol moments as compared with the thermodynamically more feasible 5-one (thione) forms (Table 2).

It is presumable that in the condensed phase the structures with an aromatic tetrazole ring should be more stabilized by intermolecular interactions and therefore their relative amount can increase.

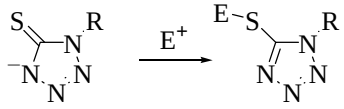
Although the thione form dominates in the neutral tetrazoles, alkylation and acylation of tetrazole-5-thione anions led to the formation of addition products exclusively at the sulfur atom (Scheme 7) [98, 99]. Therefore it is possible, that under certain conditions a considerable amount of 5-mercapto form can arise from compounds of this type.

3.3. *Other Types of Tautomerism*

Some compounds are known containing in their structure selenium and certain other elements as an exocyclic heteroatom. These compounds evidently also are capable of the appropriate types of tautomerism (Scheme 8). However these protolytic reactions are poorly understood.

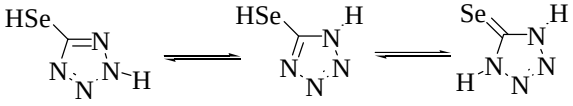
An interesting type of protolytic equilibrium involving the tetrazole ring is the tautomerism of azolotetrazoles. The best known among these compounds are pyrrolotetrazoles which may exist in different tautomeric forms. The characteristic feature of these compounds is

Scheme 7.



E = Alk, Ac.

Scheme 8.

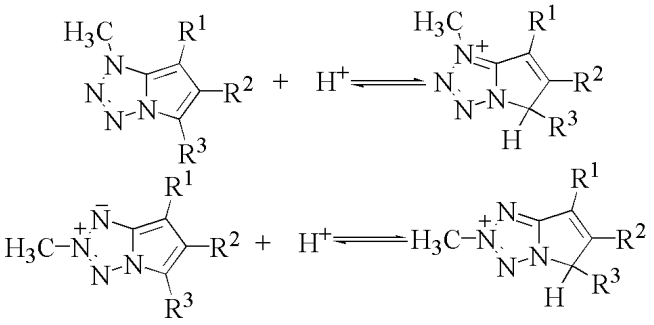


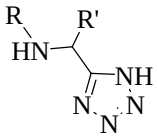
that both fused heterocycles cannot be simultaneously aromatic. The possibility was considered of tautomers existence where nonaromatic were either tetrazole or pyrrole heterocyclic fragments [100, 101]. The prevalence of certain tautomer is governed by the medium and by the character of substituents at the carbon atoms of the pyrrole ring. Some reports indicated that the pyrrolotetrazole derivatives containing donor substituents and also unsubstituted pyrrolotetrazole existed mainly in the 5*H*-form, whereas the pyrrolotetrazoles with acceptor substituents were more stable in the 1*H*-form (Scheme 9) [101, 102].

Scheme 9.

According to ^{1}H NMR (NOE) in perchloric acid the 1-methyl- and 2-methylpyrrolotetrazoles are protonated at a carbon in the position *5* (Scheme 10) [103].

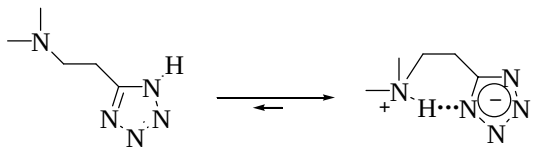
Scheme 10.





A considerable medicinal interest have tetrazole-containing amino acids analogs [104]. This type compounds alongside NH of tetrazole fragment that is sufficiently strong acid include strongly basic amino groups. Therefore in these structures a proton transfer is possible from one fragment of the molecule to another. For instance, 5-(2,2-dimethylaminoethyl)tetrazole is known to exist both in crystals and in solutions in a zwitter-ionic structure (Scheme 11) [105, 106]. Consequently, the compounds of this structure have in principal dissimilar properties compared to other tetrazoles [106].

Scheme 11.

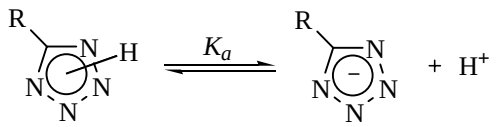


4. ACIDITY

4.1. *NH-Acidity of Mononuclear Tetrazoles*

NH-Unsubstituted tetrazoles possess acid properties (Scheme 12), whose strength depends on the electronic effect of the substituent in the position *5* [16–19]. The tetrazolate anion (tetrazolide) formed at proton cleavage is endowed with a high stability and aromaticity. This form is characterized by a high delocalization of the negative charge over the hetero ring [65]. Tetrazolides are efficient nucleophilic agents. They easily react with alkylating, acylating agents and other electrophilic species, effectively coordinate with metal ions [1, 20, 107]. Unsubstituted tetrazole exhibits the properties of an organic acid similar in acidity to acetic acid (Table 3). In general, depending on the substituent in the position *5* ionization of tetrazoles occurs in the range from–0.8 unit of H_0 scale to 7 units of pH scale. Tetrazolate anions form stable associates with proton donors. For some of these associates stability constants were estimated [108, 109].

Scheme 12.



Comprehensive studies of NH-acidity of 5-substituted tetrazoles have been performed since mid-XX century. The pK_a values were established for dozens of 5-R-tetrazoles in water solutions [13, 19] and in systems organic solvent–water [110, 111]. The quantitative measurement of the acidity constants in solutions was performed with the use of various physicochemical methods. The most resultant proved to be potentiometric titration [84, 112] and UV spectrophotometry [113].

NH-acidity values of 5-substituted tetrazoles in water solution measured experimentally are presented in Table 3 [1, 12, 13, 84, 111, 113–116]. In general the discrepancies in pK_a values obtained by different authors at the use of various experimental methods are insignificant.

Table 3. NH-Acidity constants of 5-R-tetrazoles in water at 25°C

R	pK_a	Reference
H	4.86[a]	[84]
	5.00[b]	[113]
	4.70[a]	[111][12]
	4.89[a]	
Me	5.50[a]	[84]
	5.63[a]	[13][12]
	5.56[a]	
Et	5.59[a]	[117]
i-Pr	5.53[a]	[117]
NH_2	6.00[a]	[13]
	5.93[a]	[12]
AcNH	4.49[a]	[117]
NNO_2^-	1.0[a]	[118]
CF_3	1.7[a]	[13][12]
	1.14[a]	
Ph	4.83[a]	[13]
Cl	2.07[a]	[13]
Br	2.13[a]	[13]
I	2.85[a]	[13]
NO_2	–0.83[b,c]	[84]
2-$MeOC_6H_4$	6.99[b]	[113]
4-$MeOC_6H_4$	4.75[b]	[113]
2-MeC_6H_4	4.47[b]	[113]
3-ClC_6H_4	3.77[b]	[113]
3-$NO_2C_6H_4$	3.50[b]	[113]
4-$NO_2C_6H_4$	3.45[b]	[113]
2-$NO_2C_6H_4$	3.22[b]	[113]
2-$Me_2N^+HCH_2CH_2COO^-$	3.93[a]	[106]
	5.32[a]	[119]

[a] Determined by potentiometric titration.
[b] Determined by UV spectroscopy.
[c] In water solutions of sulfuric acid using H_0 acidity function.

The pK_a values of 5-R-tetrazole (R = CH_3, H, Br, CF_3, NO_2) containing the substituent directly attached to the heterocycle correlate well with the σ_p constants of the substituents [equation (3)] [84]. The high slope value in this equation reveals the significant electronic effect of the substituent on the heterocycle.

$$pK_a = -6.65\sigma_p + 4.46;\ r\ 0.98,\ n\ 6,\ s\ 0.5. \quad (3)$$

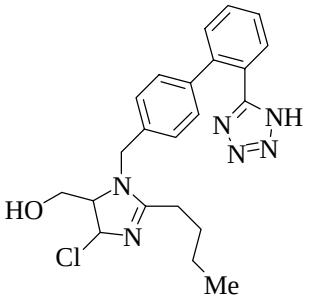
A rigorous linear relationship between the acidity constants and the substituents constants is also observed when the dissociating tetrazole ring is connected to the substituent through a benzene ring [113]. Thus the pK_a values of 5-aryltetrazoles well correlate with the σ^0 constants of substituents:

$$pK_a = -1.27\ \sigma^0 + 4.40;\ r\ 0.99,\ n\ 6,\ s\ 0.09. \quad (4)$$

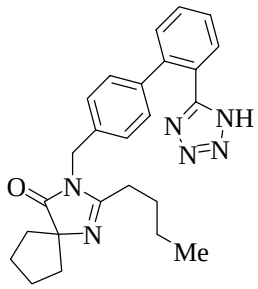
5-(2-Methoxyphenyl)tetrazole does not fit to this plot for it exhibits abnormally low acidity. It was presumed that the fact was due to the presence of a hydrogen bond of N–H···O type between the hetero ring and the oxygen of the methoxy group. Based on ρ–σ analysis it was demonstrated that the neutral tetrazole forms in the water solutions exist mainly as 1*H*-tautomers [84, 113].

It follows from equations (3) and (4) that at the acid dissociation of substituted 5-phenyltetrazoles the benzene ring to a large extent isolates the reaction center from the electronic effect of the substituent. From these equations a transmission factor was evaluated characterizing the bridging effect of the 5-phenyl substituent in this heterocyclic system, π' 0.19 [84, 113].

Fluorimetric titration in water solutions was applied to estimation of acidity constants of some well-known antihypertensive drugs containing in their structure NH-unsubstituted tetrazole fragment governing their acid properties: pK_a 3.15 (Losartan), 4.70 (Irbesartan) [120].



Losartan



Irbersartan

Thermodynamic parameters of the equilibria of acid dissociation of tetrazole, 5-methyltetrazole, and 5-trideuteromethyltetrazole calculated from the dependence of pK_a on reciprocal temperature are as follows: ΔH^0 53, 53. and 50 kJ mol^{-1}, ΔS^0 0.09, 0.07, and 0.06 J mol^{-1} K^{-1} [84]. These findings are somewhat different from analogous characteristics obtained for unsubstituted tetrazole: ΔH 14 kJ mol^{-1}, ΔS^0 –42 J mol^{-1} K^{-1} [111]. The data of the latter study are in better agreement with the results of calorimetric investigations of tetrazole: ΔH^0 13 kJ mol^{-1}, ΔS^0 –39 J mol^{-1} K^{-1} [116]. On replacement in the methyl group protium by deuterium a reversed secondary isotope effect was observed: K_H/K_D 0.9 [84].

For some tetrazoles the pK_a values were measured in mixtures organic solvent–water and in neat organic solvents [13, 110, 111, 121–125]. As expected, the pK_a values of tetrazoles in mixed solvents (water mixtures with methanol, ethanol, DMSO, DMF, and acetone) grew with increased fraction of the organic component and consequently with diminished dielectric permittivity of the medium [111, 121, 122]. For instance, the pK_a value of the unsubstituted tetrazole in DMSO was 8.23 [13].

In a lot of studies it was shown that the pK_a values of 5-R-tetrazoles correlate with various physicochemical and spectral parameters of these heterocycles [13, 16, 23, 77–80, 126–128].

The experimental value of Gibbs free energy ΔG^0 of unsubstituted tetrazole deprotonation in the gas phase determined by ion cyclotrone resonance equals 326.7 kcal mol^{-1}[129]. This value is in fair agreement with analogous characteristic calculated by DFT method in the basis B3LYP/6-31G* (324.6 kcal mol^{-1}) and fits to the general trend of variation of acid-base properties of azoles depending on their structure. Analogously, the value *PA*$^-$ 329.6 kcal mol^{-1} calculated for the anion of the unsubstituted tetrazole in the gas phase by G3 method is consistent with the experimental value (*PA*$^-$ 333.7 kcal mol^{-1}) [129, 130]. Applying theoretical methods (CBS-QB3) the values of acidity in the gas phase were also calculated for a series of 5-R-tetrazoles (R = H, Hlg, Alk, N_3, NO_2, OCH_3) [39].

In a series of publications the results were reported of quantum-chemical calculations of the anion of unsubstituted tetrazole [52, 53, 58, 131–133], of anions of some 5-R-tetrazoles [54, 57, 65, 131], and also was estimated the NH-acidity of the neutral forms. The calculations were carried out by semiempirical (CNDO, CNDO/2, MNDO, AM1, PM3) [52–54, 131, 132] and also ab initio (HF, DFT, MP2) methods with the use of various basis sets [57, 58, 65, 133]. The results of all calculations show that the tetrazolate anions (tetrazolides) are highly aromatic cyclic structures. Therefore it is partly understandable, why metal tetrazolides are very stable, and why the acidity of the tetrazole ring is extremely high.

It was shown in [65] employing DFT (B3LYP/6-31G*) method that in the case of 5-R-tetrazoles (R = H, Me, *t*-Bu, Cl, CF_3, NO_2) the protonation energy of the corresponding anions (*PE*$^-$) in the gas phase correlated well with the experimental pK_a values in water:

$$PE^- = (328.2 \pm 0.7) + (4.1 \pm 0.2)\mathrm{p}K_a;\ r\ 0.996,\ s\ 1.1,\ n\ 6. \qquad (5)$$

The same trend in variation of acid-base properties in solutions and gas phase was observed many times in nitrogen-containing heterocycles [52, 53, 55, 74, 75, 77, 127, 129].

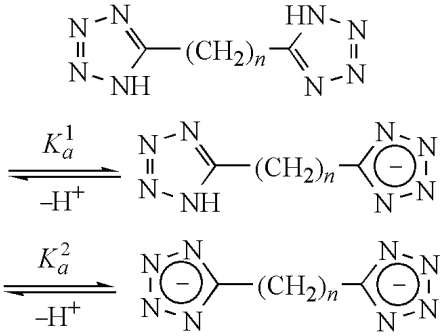
In [39, 130, 134, 135] applying theoretical methods HF and DFT, and also accounting for solvation by PCM method in the basis sets 6-31+G* and 6-31++G** were calculated pK_a values in water and other solvents for several series of 5-R-tetrazoles (R = H, Hlg, Alk, N_3, NO_2, OCH_3). For instance, the pK_a value of unsubstituted tetrazole in DMSO calculated by (IPCM/B3LYP/6-311+G(2d,p)//B3LYP/6-31G*) method differed from the experimental value by 0.6 unit [130]. Although the pK_a values calculated in this way in a number of events strongly deviate from the experimental values, this research seems very important.

4.2. *NH-Acidity of Polynuclear Tetrazoles*

Inasmuch as the polynuclear compounds containing in the molecule two or more tetrazole rings are regarded as promising complexing agents, the study of protolytic equilibria involving them is an urgent task. In [110, 112, 121, 122, 136] acidity constants were determined for several series of di-, tri-, and tetrabasic heterocyclic NH-acids.

5,5'-Bitetrazole and α,ω-ditetrazol-5-ylalkanes behave as dibasic heterocyclic NH-acids (Scheme 13).

Scheme 13.



n = 0–5.

According to [112] the 5,5'-bitetrazole is a strong dibasic acid close in the acidity value to oxalic acid (Table 4) evidencing strong electronic interaction between the rings. This is also supported by the pattern of electron absorption spectra of the compound. From the values of pK_a^1 and pK_a^2 of 5,5'-bitetrazole and the other 5-substituted tetrazoles (Table 3) σ-constants of tetrazole ring as a substituent were determined: for NH-tetrazole-5-yl

Table 4. Acid dissociation exponents of polynuclear tetrazoles in water at 25°C [112, 121][a]

Compound	pK_a^1	pK_a^2
5,5'-Bitetrazole	1.41	4.25
Di(tetrazol-5-yl)methane	3.42	5.30
1,2-Di(tetrazol-5-yl)ethane	4.42	5.74
1,3-Di(tetrazol-5-yl)propane	4.95	5.94
1,4-Di(tetrazol-5-yl)butane	5.17	6.09
1,5-Di(tetrazole-5-yl)pentane	5.23	6.10

[a] For 5,5'-bitetrazole was used UV spectroscopy, in the other cases, potentiometric titration.

group was σ_I 0.45, σ_m 0.46, for the corresponding anion, σ_I 0.12, σ_m 0.09 [137]. Tetrazolyl fragment is like a phenyl group in the character of conjugation, and like picryl group with respect to electronegativity.

Similarly, the pK_a values of α,ω-ditetrazol-5-ylalkanes (Scheme 13) with a number of methylene groups *n* from 1 to 5 are close to the corresponding characteristics of dicarboxylic acids (Table 4). [121]. A characteristic trend is observed in increasing pK_a value with the growing number of the bridging methylene groups *n*. It is expected that at $n > 5$ the pK_a^1 and pK_a^2 values would change insignificantly, and their difference would approach a statistical factor (Fig. 3).

In a system methanol–0.1 N water solution of $NaNO_3$ with methanol content from 0 to 50 wt% pK_a value of ditetrazol-5-ylalkanes changed linearly as a function of reciprocal dielectric permittivity of the medium. Besides in this series of compounds good correlations were observed of the pK_a values with the chemical shift of the endocyclic carbon of the tetrazole ring in the ^{13}C NMR spectra, and also with the chemical shift of the cabon atoms of the α-methylene groups [121].

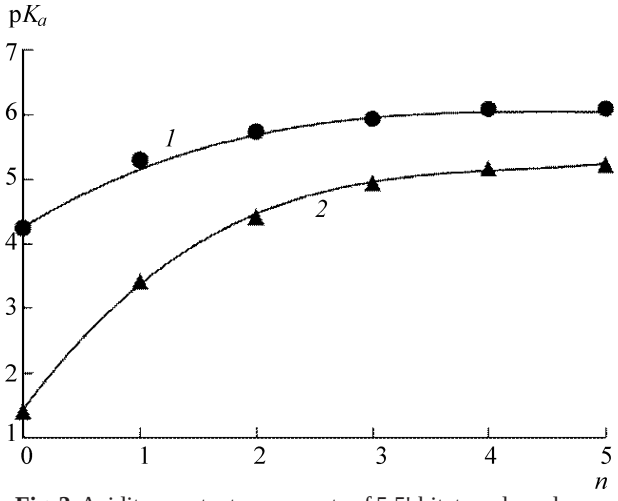
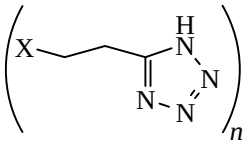


Fig. 3. Acidity constants exponents of 5,5'-bitetrazole and α,ω-ditetrazol-5-ylalkanes as a function of the number of methylene groups, (*n*): *1*, pK_a^1, *2*, pK_a^2.

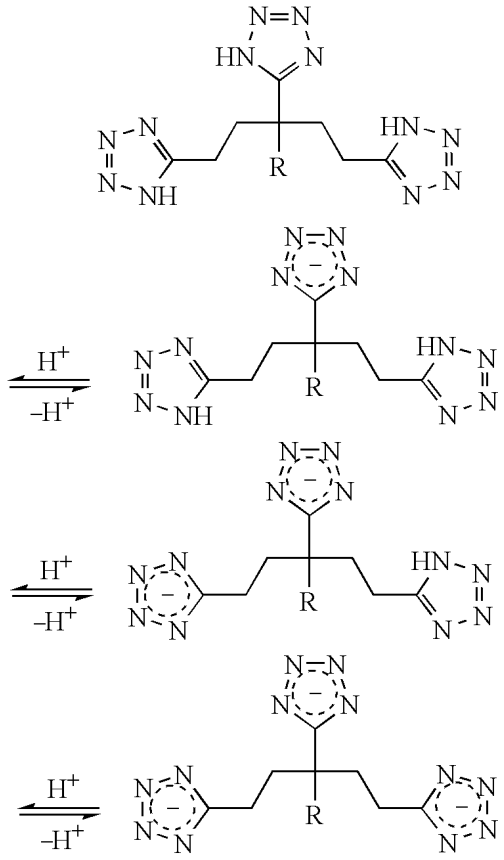
In [122] using Bjerrum distribution function pK_a^1, pK_a^2, pK_a^3, and pK_a^4 values were determined by potentiometric method for fourteen polynuclear podand-like tetrazoles in water and water-methanol solutions; the values obtained were in the range 3.5 to 7.5 pH units.



The comparison of the differences between pK_a^{n+1} and pK_a^n values of these compounds led to a conclusion that the terminal tetrazole fragments notably affect each other even at a long distance (five and more sp^3-hybridized carbon atoms). For tritetrazoles it was presumed that the tetrazole ring at a tertiary carbon atom first underwent dissociation (Scheme 14).

In some publications were given acidity constants of compounds containing in the molecule both NH-

Scheme 14.



R = H, Ar.

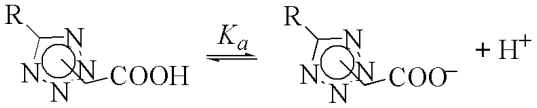
unsubstituted and N-substituted tetrazole fragments simultaneously [136, 138, 139]. NH-Acidity of these compounds is close in value to that of the corresponding derivatives of carboxylic acids.

4.3. *Other Kinds of Acidity*

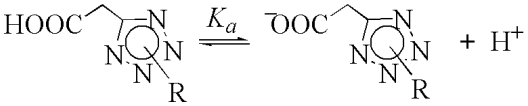
In this Section we consider the results of quantitative studies on acidity of tetrazoles when ionization occurs not at the expense of the NH group of the aromatic tetrazole ring but owing to other exocyclic functional fragments. Here the tetrazole ring affected the protolytic equilibria indirectly, as a substituent.

Ionization of three series of isomeric tetrazolylacetic acids was investigated in [119] (Table 5). In these compounds the carboxy group is capable of dissociation (Scheme 15).

Scheme 15.



R = NH_2, H, CH_3, Ar.



R = H, 1-Alk, 2-Alk.

In NH-tetrazol-5-ylacetic acid where the possibility of dissociation of the NH group in the tetrazole ring is retained just the carboxy group possesses higher acidity. The ionization of heterocycle occurs at notably lower acidity of the medium (Table 3). It was observed in this study that in water–ethanol mixtures in the range of ethanol content from 0 to 50% pK_a values of tetrazolylacetic acids changed linearly as a function of reciprocal dielectric permittivity of the medium (1/ε). All compounds under study were stronger acids than acetic acid due to electron-withdrawing effect of the tetrazole ring and they are comparable with haloacetic acids. From the data on acidity of tetrazolylacetic acids induction constants σ_I of 1-, 2-, and 5-tetrazolyl groups were calculated at 0.65, 0.62, and 0.41 respectively [119], and also σ_I-constants of 1- and 2-methyltetrazol-5-yl groups at 0.48, 0.32 respectively [137]. The acidity constants of the carboxy group tetrazole-containing analogs of natural amino acids (phenylalanine, tryptophan etc.) were measured in [136, 138, 139].

Table 5. Dissociation constants of tetrazolylacetic acids in water and 50% ethanol at 25°C measured by potentiometric titration [119]

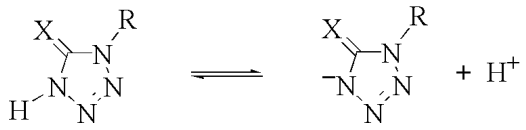
R	pK_a	R	pK_a
(5-R-tetrazol-1-yl)acetic acids			
NH_2	2.38[a]	4-ClC_6H_4	3.10
Me	2.16[a]	3-ClC_6H_4	3.13
Ph	2.11[a], 3.16	3-BrC_6H_4	3.14
4-MeC_6H_4	3.23	3-$NO_2C_6H_4$	3.05
3-MeC_6H_4	3.22	H	2.27[a]
(5-R-tetrazol-2-yl)acetic acids			
NH_2	2.60[a]	4-ClC_6H_4	3.31
Me	2.23[a]	3-ClC_6H_4	3.25
Ph	3.31	3-BrC_6H_4	3.22
4-MeC_6H_4	3.29	3-$NO_2C_6H_4$	3.28
3-MeC_6H_4	3.30	H	2.12[a]
(X-R-tetrazol-5-yl)acetic acids			
1-Me	2.83[a]	2-Me	3.44[a]
1-Et	2.85[a]	2-Et	3.45[a]
H	3.10[a]		

[a] In water.

Acidity of a series of substituted tetrazol-5-ones (thiones) was investigated [140–142]. Taking into account the conclusions presented in Section 3.2 it is presumable that in these compounds not OH or SH groups dissociate, but a nonaromatic 1,4-dihydrotetrazole (Scheme 16). The values of pK_a for some compounds of such structure were 5.53, 4.81 [1-phenyl-, 1-(4-NO_2-phenyl)tetrazol-5-ones] [140], 3.65, 3.36 [1-phenyl-, 1-(4-NO_2-phenyl)-tetrazole-5-thiones] [141, 142].

For 5-mercapto-1-methyltetrazole pK_a values were measured in water and its mixtures with various organic solvents [111]. In particular, pK_a value for this compound in water was 3.28, and thermodynamic parameters of the dissociation equlibrium were ΔH 13 kJ mol^{-1}, ΔS^0 –21 J mol^{-1} K^{-1}.

Scheme 16.



X = O, S.

Table 6. Basicity constants exponents of 5-R-NH-unsubstituted tetrazoles in water solutions of sulfuric acid at 25°C, determined by the use of UV spectroscopy (UV), ^{1}H NMR spectroscopy, Raman spectroscopy, and potentiometric titration (PT)

R	pK_{BH^+}	Method	Reference
H	–2.68	^{1}H NMR	[84]
	–3.01	Raman	[73]
Tetrazol-5-yl	–5.47	UV	[112]
	–10.91[a]		
4-MeOC$_6$H$_4$	–1.88	UV	[145]
Ph	–2.28	UV	[145]
	–2.45[b]		
	–2.32[c]		
4-ClC$_6$H$_4$	–2.51	UV	[145]
	–2.60[c]		
4-BrC$_6$H$_4$	–2.56	UV	[145]
4-IC$_6$H$_4$	–2.66	UV	[145]
3-ClC$_6$H$_4$	–2.94	UV	[145]
2-NO$_2$C$_6$H$_4$	–3.30	UV	[145]
3-NO$_2$C$_6$H$_4$	–3.38	UV	[145]
4-NO$_2$C$_6$H$_4$	–4.19	UV	[145]
	–3.40[c]		
COOH	–2.99	^{1}H NMR	[146]
Me$_2$NCH$_2$CH$_2$	9.39[d]	PT	[106]
Me$_2$N$^+$HCH$_2$CH$_2$	–2.78	^{1}H NMR	
Me	–1.83	^{1}H NMR	[84]
Br	–5.20	UV	[84]
I	–4.40	UV	[84]
CF$_3$	–7.00	UV	[84]
NO$_2$	–9.26	UV	[84]

[a] Second protonation constant calculated using acidity function H_+.

[b] At 60°C.

[c] In a system perchloric acid–water.

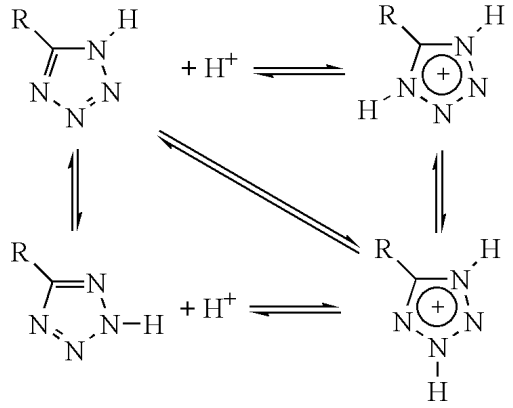
[d] For protonation at the dimethylamino group in water.

Some other kinds of equilibrium acid dissociation involving functionally-substituted tetrazoles are also known [13]. In [143] CH-acidity of the tetrazole ring in some N-substituted tetrazoles was estimated based on analysis of the isotope exchange rate of hydrogen in the endocyclic CH.

5. BASICITY

Taking into account the reasoning in Section 3.2 the protonation of the tetrazole ring may be represented by Scheme 17.

Scheme 17.



Virtually all quantitative data on the basicity of tetrazole in solution were obtained by Soviet researchers in nineteen seventies–eighties. As shown in these studies, tetrazole behave as weak bases: They are protonated only in the media whose acidity can be described by the empiric scales of acidity function. In the case of weak bases the choice of calculation method for final pK_{BH^+} values is crucially important [144]. Application of different procedures to estimation of the medium acidity and to calculation of ionization ratios can give incomparable results. It is therefore important to stress that all basicity constants given below were obtained under the same standard conditions. For the overwhelming majority of compounds under study the Hammett acidity function H_0. was used. The calculation of basicity constants was carried out by Yates and McClleland method[144].

$$\log I = -m \cdot H_0 + \mathrm{p}K'_{BH^+}, \quad \mathrm{p}K_{BH^+} = \mathrm{p}K'_{BH^+}/m, \qquad (6)$$

where I are ionization ratios determined in keeping with Stewart–Granger rule, m is slope (solvation factor) of the linear dependence of log I on the acidity of medium H_0. To exclude the influence of the solvation factor on the exponent of basicity constant pK_{BH^+} in all the cases the same formal technique was used: The ratio of the absolute term pK'_{BH^+} to the slope m was regarded as the resulting pK_{BH^+} value.

Nowadays basicity constants are known for several dozens of both NH-unsubstituted and 1- and 2-alkyl-(aryl)tetrazoles(Tables 6–8). In most cases tetrazoles possess typical properties of Hammett bases: the values of m factors in equation (6) are close to unity.

As follows from [73, 84, 106, 112, 145, 146] the protonation of 5R-NH-unsubstituted tetrazoles (Table 6) can occur in a wide range of acidity function values H_0, from –1 to –10.

The basicity constants of unsubstituted tetrazole measured by different methods are in good agreement [73, 84]. The use of Raman spectroscopy in determination of pK_{BH^+} permitted establishing that protonation of the tetrazole ring occured at the nitrogen in the position *4* [73]. This conclusion is confirmed by fair agreement of the calculated vibrational spectra and experimental one measured in the concn. sulfuric acid. A similar conclusion was made based on the results of ^{15}N NMR spectroscopy [76, 147].

Values of pK_{BH^+} of 5-R-NH-tetrazoles with substituents attached directly to the heterocycle well correlate with the σ_p constants of the substituents [84].

$$pK_{BH^+} = -7.83\,\sigma_p - 2.88;\ r\ 0.99,\ n\ 6,\ s\ 0.40. \qquad (7)$$

The slope value in equation (7) reveals the strong electronic effect of the substituent on the heterocycle. A similar substituent effect with close slope value was also observed in the relation of pK_a to σ_p(3). Equation (7) and data on the basicity of 5,5'-bitetrazole which could be protonized at one or at both heterocyclic fragments simultaneously were used to calculate the σ_p constants of a neutral and protonated tetrazol-5-yl group at 0.31 and 1.02 respectively [137].

The basicity constants of 5-aryl-NH-tetrazoles correlate well with the σ constants of the substituents in the benzene ring [145].

$$pK_{BH^+} = -1.80\,\sigma - 2.24;\ r\ 0.98,\ n\ 8,\ s\ 0.15. \qquad (8)$$

From equations (7) and (8) a transmission factor of phenyl substituent was calculated amounting to π' 0.23. A similar π' value was obtained from equations (3) and (4) describing relationship between pK_a and σ constants.

Basicity constants of certain 5-aryl-tetrazoles determined in different mineral acids (sulfuric and perchloric) have close values revealing insignificant role of solvation factors in the protonation of these compounds [145]. The 4-nitrophenyltetrazole is an exception since for this compound the difference in pK_{BH^+} values measured in sulfuric and perchloric acids amounted to 0.8 units. The latter fact is apparently due to solvation of precisely nitro group.

The same trend was observed in substituents effect on the acidity and basicity of 5-substituted tetrazoles. A good linear correlation (9) exists between the pK_{BH^+} and pK_a values [84]. This relationship is valid for a wide range of compounds and can be very useful practically.

$$pK_a = 0.78\,pK_{BH^+} + 6.37;\ r\ 0.98,\ n\ 11,\ s\ 0.3. \qquad (9)$$

Table 7. Basicity constants exponents of 1R-5R'-tetrazoles in water solutions of sulfuric acid at 25°C, determined with the use of acidity function H_0 by UV and ^1H NMR spectroscopy

Me	H	–3.00[a]	[84]
Me	Me	–1.68[a]	[84]
Me	NO_2	–9.31[b]	[84]
Me	4-$MeOC_6H_4$	–1.98[b]	[83]
Me	4-MeC_6H_4	–2.17[b]	[83]
Me	3-MeC_6H_4	–2.34[b]	[83]
Me	Ph	–2.50[b]	[83]
Me	4-ClC_6H_4	–2.75[b]	[83]
Me	4-BrC_6H_4	–2.75[b]	[83]
Me	3-$NO_2C_6H_4$	–3.63[b]	[83]
4-MeC_6H_4	H	–3.18[b]	[149]
Ph	H	–3.41[b]	[149]
4-ClC_6H_4	H	–3.70[b]	[149]
3-BrC_6H_4	H	–3.70[b]	[149]
3-ClC_6H_4	H	–3.73[b]	[149]
4-$NO_2C_6H_4$	H	–3.99[b]	[149]
4-$MeOC_6H_4$	Me	–2.19[b]	[148]
		–2.21[a]	
4-MeC_6H_4	Me	–2.11[b]	[148]
Ph	Me	–1.96[a]	[148]
4-ClC_6H_4	Me	–2.02[b]	[148]
		–2.32[a]	
3-ClC_6H_4	Me	–2.49[a]	[148]
3-$NO_2C_6H_4$	Me	–2.77[b]	[148]
4-$NO_2C_6H_4$	Me	–2.82[a]	[148]
4-$MeOC_6H_4$	Ph	–2.20[b]	[149]
4-MeC_6H_4	Ph	–2.57[b]	[149]
Ph	Ph	–2.96[b]	[149]
4-ClC_6H_4	Ph	–3.08[b]	[149]
3-ClC_6H_4	Ph	–3.20[b]	[149]
3-$NO_2C_6H_4$	Ph	–3.51[b]	[149]
4-$NO_2C_6H_4$	Ph	–3.66[b]	[149]
Me	–[d]	–6.99[a]	[152]
Ph	–[d]	–7.47[b,c]	[112]
4-MeC_6H_4	–[d]	–7.32[b]	[152]
4-ClC_6H_4	–[d]	–7.86[b]	[152]
4-BrC_6H_4	–[d]	–7.85[b]	[152]
4-$NO_2C_6H_4$	–[d]	–8.14[b]	[152]

[a] Determined by ^1H NMR spectroscopy.
[b] Determined by UV spectroscopy.
[c] Determined using acicdity function H_+.
[d] 1,1'-Disubstituted-5,5'-bitetrazole.

In 5-(2-dimethylaminoethyl)tetrazole the protonation occurs in two stages: proton addition to the nitrogen of dimethylamino group and the proper protonation of the tetrazole ring [106]. The first stage proceeds in the pH range, the second, in the region of acidity functions. The $pK_{BH^{++}}$ values of this compound calculated using various acidity functions (H_0, H_A, X) differ insignificantly.

5,5'-Bitetrazole is a considerably weaker base than unsubstituted tetrazole. The protonation of one tetrazole ring decreases the basicity constant of the other by more than 5 orders of magnitude [112]. According to the electronic spectroscopy data 5,5'-bitetrazole has a completely planar structure both in the neutral and protonated forms. The above data confirm that the tetrazole rings in this molecule in any form of existence (anion, neutral, cation) are strongly ππ-conjugated.

Several studies were dedicated to the investigation of basicity of two possible isomers of N-substituted tetrazoles [83, 84, 148, 149] (Table 7, 8). It was established that the protonation of both 1-substituted and 2-substituted tetrazoles occurred at the same basicity center, namely, by the nitrogen in the position *4* of the hetero ring [83, 84]. Note that in general the basicity of 2-substituted tetrazoles is somewhat lower as compared to that of the corresponding N*1*-isomers. This is apparently caused by different structure of conjugate acids formed on protonation, 1*H*,3*H*$^+$- and 1*H*,4*H*$^+$-forms respectively (Scheme 18). As already mentioned, the thermodynamic stability of the former is a little lower than that of the latter.

Values of pK_{BH^+} of 1- and 2-methyl-5-aryltetrazoles correlate well with the σ-constants of substituents [83].

1-methyl-5-aryltetrazoles:

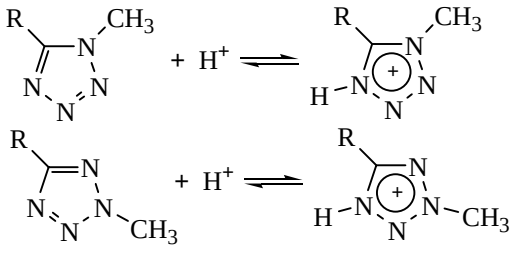
$$pK_{BH^+} = -1.63\,\sigma - 2.43;\ r\ 0.99,\ n\ 7,\ s\ 0.05, \qquad (10)$$

2-methyl-5-aryltetrazoles:

$$pK_{BH^+} = -1.25\,\sigma - 3.19;\ r\ 0.97\ n\ 10,\ s\ 0.11. \qquad (11)$$

The slope ρ in equation (10) is a bit steeper than in equation (11). Taking into account the common protonation mechanism of the compounds this fact shows that the electronic effect of the substituent on the basicity center is less in the 2-substituted tetrazoles than in the 1-isomers.

Scheme 18.



The slopes in equations (8) and (10) for NH- and 1-methyltetrazoles respectively are close. This is an additional proof that in both cases the basicity center is located on the nitrogen in the position *4*, and that the conjugate acid exists as the 1*H*,4*H*$^+$-form [83, 84]. Besides this fact evidences that in solution the NH-unsubstituted tetrazoles exist prevailingly as 1*H*-tautomer.

In [148, 149] by UV and NMR spectroscopy the protonation of three series of 1-aryltetrazoles (1-aryltetrazoles, 1-aryl-5-methyltetrazoles, and 1-aryl-5-phenyltetrazoles) was shown to be well described by Hammett acidity function H_0. Good to fair correlations were observed for all the three series of heterocycles of the basicity constants exponents with the constants of substituents: for 1-aryltetrazoles and 1-aryl-5-methyltetrazoles with the inductive constants σ_I [equations (12, 13)], and for 1-aryl-5-phenyltetrazoles with σ-constants [equation (14)].

1-aryltetrazoles [149]:

$$pK_{BH^+} = -0.85\,\sigma_I - 3.39;\ r\ 0.96,\ n\ 6,\ s\ 0.09 \qquad (12)$$

1-aryl-5-methyltetrazoles [148]:

$$pK_{BH^+} = -1.17\,\sigma_I - 1.96;\ r\ 0.95,\ n\ 7,\ s\ 0.11 \qquad (13)$$

1-aryl-5-phenyltetrazoles [149]:

$$pK_{BH^+} = -1.20\,\sigma - 2.74;\ r\ 0.97,\ n\ 7,\ s\ 0.13 \qquad (14)$$

Table 8. Basicity constants exponents of 2-methyl-5-R-tetrazoles in water solutions of sulfuric acid at 25°C, determined with the use of acidity function H_0 by UV spectroscopy [83, 84]

R	pK_{BH^+}
H	–3.25[a]
N++	–9.06
4-$MeOC_6H_4$	–2.72
4-MeC_6H_4	–2.90
3-MeC_6H_4	–3.20
2-MeC_6H_4	–3.18
Ph	–3.27
4-ClC_6H_4	–3.46
4-BrC_6H_4	–3.41
3-BrC_6H_4	–3.89
3-$NO_2C_6H_4$	–3.99
4-$NO_2C_6H_4$	–4.10

[a] Determined by ^{1}H NMR spectroscopy.

The slopes of the linear dependences (12–14) are considerably less than in equations (8) and (10). This shows the notably weaker transmission of the electronic effect of substituent through the phenyl group attached to the position *1* of the heterocycle than through a phenyl in the position *5*.

According to the data of X-ray diffraction analysis, NMR and Raman spectroscopy, and theoretical calculations by methods MP2 and DFT in the basis 6-31G* the protonation of 1,5-diaminotetrazole occurred at the nitrogen of the heterocycle in the position *4* but not at the amino group [150, 151]. As shown in [112, 152], 1,1'-disubstituted-5,5'-bitetrazoles are even weaker bases compared with NH-unsubstituted 5,5'-bitetrazoles (Table 7).

The protonation of isomeric 1*H*-, 2*H*- , and 5*H*-tetrazolylacetic acids was studied by IR, UV, and ^{1}H NMR spectroscopy (Table 9) [146]. According to the data of vibrational spectroscopy, the protonation of these compounds at the carboxy group was not observed even in concn. sulfuric acid. As with *N*-methyl(aryl)tetrazoles, the proton added to all these compounds at the nitrogen of the heterocycle in the position *4*. The process is described by Scheme 19. The values of pK_{BH^+} of tetrazolylacetic acids were determined at the use of both Hammett acidity function H_0 and an excess acidity function *X*. For all compounds under study the application of both functions gave virtually identical results. The values of pK_{BH^+} of 5-aryl-1*H*- and 5-aryl-2*H*-tetrazolyl-acetic acids are in good correlation with the σ-constants of substituents:

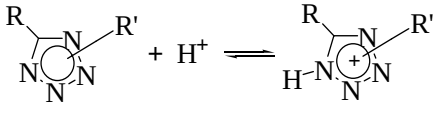
$$pK_{BH^+} = -1.53\,\sigma - 3.26;\ r\ 0.98,\ n\ 8,\ s\ 0.12, \quad (15)$$

$$pK_{BH^+} = -1.50\,\sigma - 4.16;\ r\ 0.98\ n\ 8,\ s\ 0.13. \quad (16)$$

Unlike 1- and 2-methyl-5-aryltetrazoles [equations (10) and (11)] the slopes of straight lines (15 and 16) have similar magnitude.

The quantitative parameters characterizing the basicity of unsubstituted tetrazole in the gas phase were determined by the method of ion cyclotrone resonance: *PA* 198.2, *GB* 190.2 kcal mol^{-1} [129, 153]. These constants fit well to the general trend in variation of acid-base characteristics of aromatic nitrogen-containing heterocycles depending on their structure and spectral properties [79]. The attempt to determine by this method the basicity of 5-nitrotetrazole in the gas phase failed due to its instability under the experimental conditions [71]. In [154–156] thermodynamic parameters were presented characterizing the basicity of tetrazole ring with respect to lithium cation in the gas phase obtained by experimental (ion cyclotrone resonance) and theoretical [G2, G2(MP2), B3LYP/6-31+G**] methods.

Scheme 19.



R = H, Ar.

Table 9. Basicity constants exponents of 5-R-1*H*- and 5-R-2*H*-tetrazolylacetic acids in water solutions of sulfuric acid at 25°C, determined with the use of acidity function H_0 by UV spectroscopy [146]

R	pK_{BH^+}	R	pK_{BH^+}
(5-R-1-tetrazolyl)acetic acids			
H	–3.65[a]	4-BrC_6H_4	–3.63
4-MeC_6H_4	–2.95	3-ClC_6H_4	–3.65
3- MeC_6H_4	–3.03	3-$NO_2C_6H_4$	–4.40
Ph	–3.44	4- $NO_2C_6H_4$	–4.41
4-ClC_6H_4	–3.73		
(5-R-2- tetrazolyl)acetic acids			
H	–4.53[a]	4-BrC_6H_4	–4.54
4-MeC_6H_4	–3.74	3-ClC_6H_4	–4.97
3- MeC_6H_4	–4.05	3-$NO_2C_6H_4$	–5.19
Ph	–4.13	4- $NO_2C_6H_4$	–5.22
4-ClC_6H_4	–4.50		

[a] Determined by ^{1}H NMR spectroscopy.

In numerous studies the basicity of tetrazoles in the gas phase was calculated by theoretical methods [52, 53, 58, 65, 71, 74, 75, 144]. Practically all the studies considered only the simplest member of this heterocyclic series, unsubstituted tetrazole. Quantum-chemical calculations were done both by semiempirical [52, 53, 74, 75, 144, 152] and ab initio procedures [58, 65, 71, 74, 144]. In the nonempirical calculations the protonation of tetrazole essentially depended on the chosen basis set [58]. Although the application of the ab initio calculations is more proper, the semiempirical procedures make it possible to reveal on the qualitative level the general trends in variation of properties depending on the compound structure [52, 53, 74, 75, 152]. For instance, the proton affinity in the gas phase *PA* calculated by semiempirical methods fairly were correlate with the experimental findings [52, 53, 74, 75].

The investigation of the effect of a substituent in the ring on the protonation energy *PE* calculated on the level B3LYP/6-31G* for a series of 5-R-tetrazoles (R = H, Me, *t*-Bu, Cl, CF_3, NO_2) was carried out in [65]. The

protonation energies of 2*H*-forms of neutral tetrazoles giving 1*H*,3H^+-forms of conjugate acids correlate with pK_{BH^+} and σ_p values [equations (17 and 18)]. However the correlation factor for these relationships is not high.

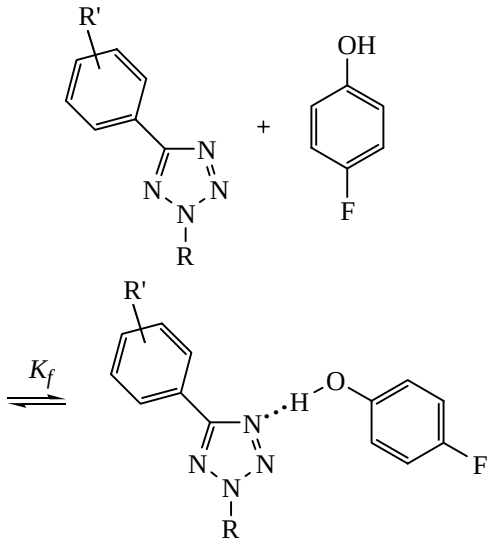
$$PE = 220.2 + 3.1pK_{BH^+}; r\ 0.963, s\ 3.0, n\ 6, \quad (17)$$

$$PE = 211.3 - 24.5\ \sigma_p; r\ 0.968, s\ 2.8, n\ 6. \quad (18)$$

A single publication contained an attempt to calculate the thermodynamic value of pK_{BH^+} for unsubstituted tetrazole in solutions applying exclusively theoretical methods (G3 for calculationg energy and PCM, iLD, PB accounting for solvation) [72]. The calculated pK_{BH^+} values significantly deviated from the experimental ones.

In [157] by Fourier IR spectroscopy the dissociation constants exponents of complexes with hydrogen bonds were determined at pK_{HB} 0.9–1.3 for a series of 2-alkyl-5-aryltetrazoles and *p*-fluorophenol in tetrachloromethane solution (Scheme 20). The electronic effect of substituents on the pK_{HB} value of tetrazoles is insignificant. These compounds exhibit the properties of hydrogen bond acceptors of medium strength comparable to those of diazines. The difference in pK_{HB} value of the tetrazole ring and of strongly basic azines and azoles are not so pronounced as in the pK_{BH^+} values. This fact may be due to the following: When a complete proton transfer occurs, it is governed apparently by the thermo-dynamic stability of the conjugate acid, whereas on formation of the complex with a hydrogen bond the crucial importance can obtain the charge on the nitrogen atom and its sterical accessibility. The thermodynamic parameters of the equilibrium shown in Scheme 20 were determined for 2-isopropyl-5-phenyltetrazole at 298 K: ΔH –12.4 kJ mol^{-1}, ΔS^0 –20 J mol^{-1} K^{-1}.

Scheme 20.



Thus the analysis of published data shows that nowadays a sufficiently vast experimental and theoretical information exists on acidity, basicity, and tautomerism of tetrazoles. By various methods not only dozens of fundamental constants were determined for compounds of this series, but the effect thereto of different factors was analyzed. In the framework of this research the opportunity was demonstarated of the modern complex approach to the protolytic equilibria of heterocycles, including both versatile experimental and theoretical methods. This approach makes it possible to draw a complete pattern of behavior of a definite series of organic compounds under various conditions

We believe that the promising research direction in the field of protolytic equilibria in compounds of the tetrazole series is an investigation of the so-called incomplete equilibria, e.g., hydrogen bonding, and also the equilibria involving polynuclear systems containing two or more tetrazole rings in the structure.

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